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Claim 17 has been rejected under 35 U.S.C. § 101 as being drawn to non-statutory subject matter. Claim 17 has been amended to change “mammal” to --rat--. Support for this amendment may be found on page 12, line 22.

✓ Claim 12 is objected to as being in improper form. Claim 12 has been canceled.

✓ Claims 9 and 11 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material recited in the claims. A Declaration identifying that a deposit has been made is submitted with this response. Claim 11 has been canceled.

Applicants submit that claim 9 now satisfies the requirements of 35 U.S.C. § 112.

Claims 1-11, 13, 17 and 21-24 are rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification does not enable the full scope of the claims. Applicants respectfully submit that the amendments to claims 1, 3, 4, 13, 17, and 21-24, which change recitation of “mammal” to ~~–rat–~~ and delete reference to mammary, liver, and kidney cell lines, obviate this rejection.

Claims 1-8, 10, 14-16, and 21-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner objects to the use of the word “derived” in claims 1-8 and 10, the term “regular supply” in claims 14-16, and the term “the invention” in claims 21-24. The Examiner also contends that the recitation in claim

16 of “from 2 mg to 8 mg” renders the claim indefinite because the duration and intervals of such a dose are not defined.

Claims 1-8 and 10 have been amended to recite --obtained-- instead of “derived.” Claim 14 has been canceled. Dependent claims 15-16 now depend on claim 13, which does not recite “regular supply.” Claims 21-24 have been amended and no longer recite “the invention.” Claim 16 has been amended to recite that the FSH dosage is administered over a 1 to 4 day time period. Support for this amendment can be found on pages 14 and 22. Applicants respectfully submit that the amended claims satisfy the requirements of 35 U.S.C. § 112, second paragraph.

Support for new claims 25 to 27 may be found throughout the application and, in particular, on pages 8-9 and 17-18. Support for new claim 28 can be found in claim 19. Support for new claim 29 can be found in original claim 20.

### **35 U.S.C. § 102 Rejections:**

#### **Leder:**

Claims 1-3, 5, 17, and 19-24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Leder et al. (U.S. Patent No. 5,087,571). The Examiner contends that Leder teaches a method of providing a cell line from a transgenic non-human mammal encoding a transforming oncogene operably linked to a mammary specific promoter, MMTV. The Examiner further asserts that Leder teaches the use of the transgenic animal for testing a

material suspected of being a carcinogen and for testing a material for its ability to confer protection against the development of neoplasms using transgenic animals.

Applicants respectfully disagree. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. M..P.E.P. § 2131. There must be no difference between the claimed invention and the reference disclosed, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v Genentech, Inc.*, 927 F.2d 1565, 118 U.S.P.Q.2d 1001, 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991).

The Leder reference does not teach every limitation present in claims 1-3, 5, 17, and 19-24.

The oncogene in Leder et al. is an activated oncogene, not a conditional oncogene, transforming gene, immortalizing gene, or cell cycle affecting gene as required by the present claims. The transgenic animals disclosed in Leder are mice, not transgenic rats as required by the amended claims. Furthermore, Leder does not teach the use of a cell type specific promoter.

In addition, contrary to the Examiner's assertion, Leder et al. does not teach the generation of conditionally immortalized cell lines. Leder merely states that the transgenic animals of the invention can be used as a source of cells for cell culture and that cells of tissues carrying the genes can be cultured. *See* Col. 9, lines 11-20. This bald assertion is not an enabling disclosure of the generation of cell lines obtained from a

transgenic rat comprising a conditional oncogene, transforming gene, immortalizing gene, or a cell cycle affecting gene operably linked to a cell type specific promoter. *See M.P.E.P. § 2121.01* citing *In re Hoeksema*, 399 F.2d 269 (C.C.P.A. 1968) (In determining what quantum of prior art disclosure is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling' disclosure.").

Therefore, the Leder reference does not anticipate the claimed invention because it does not teach each and every element of Applicants' claims. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b) in view of Leder et al.

**Reeben:**

Claims 1, 3, and 4 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Reeben et al. (Biochem. Biophys. Res. Com. 192(2):466-470, 1993). The Examiner alleges that Reeben et al. teaches tissue specific expression using a rat light neurofilament (NF-L) promoter to drive the expression of a reporter gene. The Examiner also contends that elements i) and ii) of claim 1 are not required to be either linked to each other or be linked to a transgene in the cell.

Claim 1 has been amended to require that element i) is operably linked to element ii). Thus, this rejection has been obviated.

Moreover, the Reeben reference does not anticipate the claimed invention because the reference does not teach each and every limitation of the claims. Reeben et al. produced transgenic mice carrying either a 5 kbp or 407 bp fragment of the rat neurofilament gene linked to the chloramphenicol acetyltransferase gene.

Reeben does not teach a cell line derived from a transgenic rat comprising a conditional oncogene, transforming gene, immortalizing gene, or a cell cycle affecting gene operably linked to a cell specific promoter as presently claimed. Moreover, Reeben et al. does not refer to cell lines derived from any animal. The lines referred to in the Reeben paper are transgenic mice strains and not cell lines. Furthermore, no cell lines could be obtained from these mice since the construct, before introduction into the mice, does not contain an immortalizing gene.

In addition, Reeben uses a rat NF-L promoter in mice cells. In contrast, present claim 4 requires human NF-L promoter in rat cells.

Reeben clearly identifies the problems of obtaining rat cell-type specific expression in culture using an NF-L promoter, stating “[p]reviously, several groups have studied NF-L promoter driven reporter genes or transient expression of complete NF-L genes in different cell lines, particularly in rat pheochromocytoma PC12 cells, C6 glioma cells, and fibroblasts. No cell-type specific expression was observed.” Reeben at page 465. This language suggests that an NF-L promoter would not be useful for specific immortalization purposes using rat cells. Furthermore, the 5kb rat NF-L promoter used in

Reeben is not tissue specific, but gives rise to expression in muscle and eyes, as well as nerves, of mice. Therefore, it is an unexpected result that the 6kbp fragment of the human

*1/10  
dbr* NF-1 promoter, when introduced into transgenic rats, as opposed to mice, would result in a completely unique tissue specific expression for the brain in the resultant transgenic rat.

See Application, Table 2, page 28.

Thus, in view of the foregoing remarks and amendments, Applicants respectfully submit that none of the claims are anticipated by Reeben et al. and respectfully request withdrawal of the rejection under 35 U.S.C. §102(b) in view of Reeben et al.

**Noble:**

Claims 1, 3, 5, and 6 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Noble et al. (WO 91/13150, 1991). The Examiner contends that Noble et al. teaches transgenic animals and tissue specific cell lines obtained from the animal, wherein the cell line comprises the SV40tsA58 immortalizing gene.

Applicants respectfully traverse. As noted by the Examiner, Noble et al. does not disclose the use of a cell type specific promoter in combination with the conditional ? oncogene. See page 9 of the Office Action. (“However, Noble et al does not teach the regulation of a transgene using a cell type specific promoter.”). Since claims 1, 3, and 6

each require a cell type specific promoter, and Noble et al. does not teach a cell type specific promoter, Noble does not anticipate the claims.

Furthermore, Noble et al states “[t]he rationale behind the use of a controllable, non-constitutive promoter is to inhibit the expression of the gene of interest, except when such expression is desired.” Noble et al. Page 25, lines 28-29. Noble goes on to state that “[n]on-constitutive promoters which are useable in the present invention are regulatable by changing the conditions. Under certain conditions (non-permissive) the promoter function is inhibited and normal cellular development takes place. If their conditions are changed (e.g. in the example referred to above by exposure to gamma interferon) to be permissive appreciable expression occurs. Avoiding appreciable expression is critical . . .”

Page 29, lines 1-6, continues on to say “[t]he MMTV promoter, which is regulated by glucocorticoids is an inducible promoter which has been used in transgenic experimentation. This promoter, however, suffers from the liability that endogenous glucocorticoids production would activate expression of a differentiation inhibiting construct.”

These passages are not an anticipatory disclosure of a construct comprising a cell type specific promoter and a conditional oncogene, or even of a construct comprising a MMTV promoter and a conditional oncogene. It is merely a statement that the MMTV promoter has been used in transgenic experimentation. There is no specific

teaching of the use of the MMTV in combination with a conditional oncogene. Furthermore, this teaching clearly states that using the MMTV promoter (which is noted to be an inducible promoter but is not a truly non-constitutive promoter since low levels may be permanently expressed in the body) would not be suitable. One aspect of the present invention resides in the use of the conditional oncogene, transforming gene, immortalizing gene or a cell cycle affecting gene to control expression as opposed to relying solely on a conditional promoter.

In view of the foregoing amendments and remarks, Applicants submit that Noble et al. does not anticipate the claimed invention because it does not disclose each and every element of Applicants' claims. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b) in view of Noble et al.

**Moses or Stocklin:**

Claims 1-5 and 7 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Moses JH (Br. J. Cancer. 69(21):1, 1994) or Stocklin et al (J. Cell Bio. 122(1):199-208, 1993). The Examiner contends that Moses teaches a transgenic mouse expressing a gene encoding huTGF- $\alpha$  under the control of MMTV enhancer/promoter in mammary cells and that Stocklin et al. teaches a transgenic mouse wherein the C-erb-2 is operably linked to MMTV enhancer/promoter sequence such that the transgene is expressed in a variety of cell lines.

Applicants respectfully traverse. Both Moses and Stocklin et al. discuss transgenic mice and an MMTV LTR promoter/enhancer region. The present amended claims do not contain these limitations. Further, neither Moses nor Stocklin teach a cell type specific promoter. As stated in Stocklin p.201, “[d]espite the implication in its name, the MMTV LTR is not exclusively active in mammary gland cells. High level of expression have been detected in mammary epithelium, but expression was also found in the epithelial cells of salivary glands, lung, kidney, seminal vesicles, testes, and also in lymphoid cells in spleen and thymus.” (Emphasis added). Further, the expression in Stocklin et al. is not specific since expression of the transgene was observed in the kidney, lung, mammary gland, salivary gland, and in the epithelial cells of the male reproductive tract.

In view of the foregoing remarks and amendments, Applicants submit that claims 1-5 and 7 are not anticipated by Moses or Stocklin and respectfully request withdrawal of the rejection under 35 U.S.C. §102(b).

**35 U.S.C. S 103 Rejections:**

**Noble in view of Stocklin and Reeben:**

Claims 1 and 8-11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Noble et al. in view of Stocklin and further in view of Reeben et al. The Examiner asserts that Noble teaches making cell lines from the tissue of a non-human

transgenic animal encoding the SV40tsA58 gene, but acknowledges that Nobel does not teach the regulation of a transgene using a cell type specific promoter. The Examiner also asserts that Stocklin teaches a transgenic mouse wherein the transforming human c-erb-2 is operably linked to the MMTV enhancer/promoter sequences such that the transgene is expressed in a variety of cells, and that Reeben et al. teaches tissue specific expression of a rat NF-L promoter to drive expression of a reporter gene in transgenic mice. The Examiner contends that it would have been obvious to use the MMTV promoter sequence of Stocklin et al. with Noble et al.'s teaching of making tissue specific cell lines from a transgenic animal with Reeben et al.'s teaching of a NF-L promoter to make a transgenic rat encoding a tissue specific promoter operably linked to a SV40tsA58. The Examiner also contends that one would have been motivated to derive a tissue cell line from a transgenic animal, because the cell harbors the characteristic of tissue specific markers.

Applicants respectfully disagree with the Examiner's rejection and submit that the claimed invention is not rendered obvious by the cited art using the objective standard for obviousness under 35 U.S.C. § 103(a). A finding of obviousness under §103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

*Graham v Deere*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). To establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art.

M.P.E.P. § 2143.03. Thus, the relevant inquiry is whether the prior art suggests each of the claim limitations of the invention, whether the prior art provides a motivation to combine the references, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, (Fed. Cir. 1988).

In the present instance, the relevant inquiry is whether the Noble reference, when taken with Stocklin and Reeben, suggests the claimed invention and whether the cited references themselves provide one of ordinary skill in the art with the motivation to combine them and a reasonable expectation of success of generating a cell line obtained from a transgenic rat comprising a conditional oncogene, transforming gene, immortalizing gene, or a cell cycle gene operably linked to a cell type specific promoter. Applicants assert that the cited references neither suggest the claimed subject matter of the invention, nor do they provide a motivation to combine the references. Moreover, the references do not provide any expectation of success in achieving the claimed invention.

The examiner has cited no evidence that anyone has produced a transgenic animal with a cell specific promoter operably linked to a conditional oncogene, transforming gene, immortalizing gene, or a cell cycle affecting gene.

In addition, Applicants disagree with the Examiner's assertion that Nobel teaches the making of tissue specific cell lines from a transgenic animal. As described above, Noble does not teach making a cell line from a transgenic animal comprising a cell-

type specific promoter operably linked to a conditional oncogene. Noble clearly states that all of the cells in the animals will express the immortalizing gene when stimulated. Noble further states that this lack of tissue specificity is an advantage of their invention because it means that any of the animal's cells can, in principle, be immortalized. *See* M.P.E.P. § 2143.01 which states that the proposed claimed modification cannot render the prior art unsatisfactory for its intended purpose. If the claimed tissue specific promoters were used in Noble's animal, then the animal would be unsatisfactory for its intended purpose of having all cells immortalized.

Furthermore, Applicants respectfully disagree with the Examiner's assertion that it would have been obvious to use an NF-L promoter to derive tissue specific expression of a transforming gene. As set forth above in response to the Examiner's § 102 rejection in view of Reeben, it would not have been obvious to select the human NF-L promoter recited in claim 8 as a cell specific promoter in rat cells. Reeben identifies the problems of obtaining rat cell-type specific expression in culture using an NF-L promoter. Reeben et al. states “[p]reviously, several groups have studied NF-L promoter driven reporter genes or transient expression of complete NF-L genes in different cell lines, particularly in rat pheochromocytoma PC12 cells, C6 glioma cells, and fibroblasts. No cell-type specific expression was observed.” Reeben at page 465. This language suggests that the NF-L promoter would not be useful for specific immortalization purposes using rat cells. Furthermore, the 5kb rat NF-L promoter used in Reeben is not tissue specific but

gives rise to expression in the muscle and eyes, as well as nerves, of mice. It is an unexpected result that the 6kb fragment of the human NF-1 promoter, when introduced into transgenic rats, as opposed to mice, would result in a completely unique expression for the brain in the resultant transgenic rat. See Application, Table 2, page 28.

The Examiner has not provided evidence that one of ordinary skill in the art, using the teachings of Noble, Stocklin, and Reeben would be able to produce the claimed invention.

None of the references teach a transgenic rat, the use of cell type specific promoter in a rat, as required by the amended claims.

In view of the foregoing remarks and amendments, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b)/103 rejection under Noble, Stocklin, and Reeben.

**Hammer in view of Leder:**

Claims 13-17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hammer et al. (U.S. Pat. No. 5,489,742) in view of Leder et al. The Examiner asserts that Hammer teaches a method a method for preparing transgenic rats by superovulating a female rat by continuous supply of FSH followed by the introduction of a transgene into the fertilized egg and that Leder teaches a transgenic mouse encoding a transforming oncogene operably linked to mammary specific promoter MMTV LTR.

Thus, the Examiner contends that because Hammer teaches a method of producing transgenic rats by superovulating female rats with FSH and Leder teaches a transgenic mouse with a transforming oncogene, it would have been obvious to one of ordinary skill in the art to produce transgenic rats by superovulating female rats, wherein the transgenic rat expresses an oncogene.

Applicants respectfully traverse. As discussed above, beginning on page 8, Leder et al. teaches an activated oncogene. Leder does not teach or suggest use of a conditional oncogene, transforming gene, or immortalizing gene, as required by the claims. To establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art. M.P.E.P. § 2143.03. Leder does not teach or suggest every element of the claims. Hammer does not cure this defect in Leder. Therefore, Applicants submit that the claimed invention is not obvious over Hammer et al. in view of Leder et al. and respectfully request withdrawal of the section 103 rejection.

**Hammer in view of Moses or Stocklin:**

Claims 17 and 18 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hammer et al. in view of Moses (Br. J. Cancer. 69(21):1, 1994) or Stocklin et al. The Examiner contends that Hammer teaches a method for preparing transgenic rats by superovulating a female rat by continuous supply of FSH followed by the introduction of a transgene into the fertilized egg. The Examiner also contends that

Moses teaches a transgenic mouse expressing a gene encoding hu-TGF-a under the control of MMTV enhancer/promoter (page 1, s.1) and that Stocklin teaches a transgenic mouse wherein the human c-erb-2 is operably linked to MMTV enhancer/promoter sequence. Thus, the Examiner contends that it would have been obvious to make a transgenic rat expressing TGF-a and c-erb-2 by combining Hammer et al.'s teaching of a method of making a transgenic rat with Moses or Stocklin's teaching of making transgenic mice expressing TGF-a and c-erb-2. The Examiner also contends that one would have been motivated to have a transgenic rat expressing the same transgene as a transgenic mice because rats are widely used in biomedical research.

Applicants respectfully traverse. As described above in response to the Examiner's section 102 rejection under Moses or Stocklin, both Moses and Stocklin et al. discuss transgenic mice and an MMTV LTR promoter/enhancer region. The present amended claims do not contain these limitations. Further, neither Moses nor Stocklin teach a cell type specific promoter. As stated in Stocklin p.201, "[d]espite the implication in its name, the MMTV LTR is not exclusively active in mammary gland cells. High level of expression have been detected in mammary epithelium, but expression was also found in the epithelial cells of salivary glands, lung, kidney, seminal vesicles, testes, and also in lymphoid cells in spleen and thymus." (Emphasis added). Further, the expression in Stocklin et al. is not specific since expression of the transgene was observed in the kidney,

lung, mammary gland, salivary gland, and in the epithelial cells of the male reproductive tract. Hammer does not cure these defects in Moses or Stocklin.

In addition, the Examiner has not established a reasonable expectation of success. As stated in M.P.E.P. § 2143.02, the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. The Examiner has not provided evidence that one of ordinary skill in the art, using the teachings Stocklin, Moses, and Hammer would be able to produce the claimed invention.

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

If there are any other fees due in connection with filing of this response, please charge the fees to our Deposit Account No. 02-4377. If a fee is required for an

extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 02-4377.

Respectfully submitted,



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